Study protocol

“MinimALL“

i**M**ag**IN**g of chemotherapy-**I**nduced **M**orphological and functional lung changes in childhood **A**cute **L**ymphoblastic **L**eukemia and Hodgkin`s disease

Trial Short Title	MinimALL
Trial Full Title	i**M**ag**IN**g of chemotherapy-**I**nduced **M**orphological and functional lung changes in childhood **A**cute **L**ymphoblastic **L**eukemia and Hodgkin`s disease
Funding	Internal
Trial Principle Investigator	Dr. med. A. Karow PD Dr. med. F. Knieling
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Document Version	1.8
Document Version Date	11.12.2024
NCT-Number	06093334

1. Table of content

2. Study title, version number, version date

Study title

i**M**ag**IN**g of chemotherapy-**I**nduced **M**orphological and functional lung changes in childhood **A**cute **L**ymphoblastic **L**eukemia and Hodgkin`s disease

Version

Version 1.8

Version date

11.12.2024

Protokollversionen

Date	Version	Status	Changes
08.11.2022	1.0	Draft	
10.11.2023	1.1	Draft	Inlusion of HSCT patients
25.01.2023	1.2	Final	Inclusion of cardiopulmonary testing
16.02.2023	1.3	Formal revisions according to Ethics Committee	
20.02.2023	1.4	Additional formal revisions according to Ethics Committee	
30.03.2023	1.5	Substantive revisions according to Ethics Committee	
27.04.2023	1.6	Amendment	Inclusion of patients with Hodgkin`s disease
11.08.2023	1.7	Amendment	Complementation of echocardiography and strain analysis Addition of people conducting the study
11.12.2024	1.8	Addition of missing information	Addition of the missing NCT Number on the cover page

3. Project summary

With increasing cure rates of childhood cancer there is growing recognition of late effects of treatments. However, there is a lack of non-invasive and child-friendly procedures that can indicate possible late damage. This study uses morphologic and free-breathing phase-resolved functional low-field (PREFUL) magnetic resonance imaging (MRI) to identify persistent pulmonary toxicity after treatment for childhood acute lymphoblastic leukemia (ALL), Hodgkin`s disease (HD) and allogeneic stem cell transplantation.

4. Responsibilities

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Funding

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5. Scientific background

Currently, overall cure rates of therapy for childhood acute lymphoblastic leukemia (ALL) and Hodgkin`s disease (HD) exceed 80% [1]. Apart from the development of supportive measures and novel targeted therapies, this success is still based largely on the optimized and risk-adapted dosing and scheduling of conventional chemotherapeutic agents and addition of radiotherapy in patients with HD in case of suboptimal response. Even though, contemporary systemic and local treatment regimens are less intensive than previous therapies, they are still associated with diverse general and specific, acute and chronic organ toxicities such as cardiac dysfunction, osteonecrosis, neurocognitive impairment, and second malignant neoplasms [2]. With increasing cure rates has come growing recognition of such adverse late effects of treatment and a number of guidelines for long-term follow-up (LTFU) after childhood cancer therapy have been proposed [3]. During treatment and aftercare, however, only crude orienting investigations assessing organ function are foreseen by these recommendations and apart from physical examinations and laboratory analyses, echocardiography remains the only functional imaging measure routinely applied according to the current protocols for pediatric ALL and HD. It appears conceivable, that by such investigations, minor organ alterations could be missed and additional approaches comprising more sensitive structural or functional imaging would be essential to facilitate early recognition and possible timely management of developing still subclinical alterations.

We here hypothesize that morphologic and free-breathing phase-resolved functional low-field (PREFUL) MRI may identify persistent pulmonary toxicity after treatment for childhood ALL and HD, respectively. Therefore, we propose to perform a cross-sectional, prospective, single-center clinical pilot study using low-field MRI in children and adolescents during the first five years after the end of therapy. The results of this trial could contribute to the implementation of further investigation techniques in future standardized and structured LTFU care.

References

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2. Silverman LB. Balancing cure and long-term risks in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2014;2014(1):190-7. Epub 2015/02/20. doi: 10.1182/asheducation-2014.1.190. PubMed PMID: 25696854.
3. Gebauer J, Baust K, Bardi E, Grabow D, Stein A, van der Pal HJ, et al. Guidelines for Long-Term Follow-Up after Childhood Cancer: Practical Implications for the Daily Work. Oncol Res Treat. 2020;43(3):61-9. Epub 2020/01/14. doi: 10.1159/000504200. PubMed PMID: 31931503.

6. Study aims

Determination of the frequency of morphologic and functional lung parenchymal changes using low-field magnetic resonance imaging

Hypotheses:
- Lung parenchymal changes can be detected in pediatric and adolescent patients after completion of chemotherapy or chemotherapy and additional radiotherapy
- Patients with changes do not present with clinical symptoms

Primary Objective:
- To determine the frequency of morphologic lung parenchymal changes using LF-MRI.

Secondary Objectives:
- To determine the frequency of functional lung parenchymal changes using LF-MRI.
- Determination of the anamnestic frequency of clinical respiratory symptoms
- To assess myocardial function by echocardiographic strain and strain-rate imaging

Study type
Prospective, monocentric, diagnostic study

7. Target variables

Primary target variables:

LF-MRT	Changes of lung parenchyma

Secondary target variables:

LF-MRT	Functional lung parameters (Ventilation match/mismatch, Perfusion match/mismatch, combined defects)
Cardiopulmonary testing	Oxygen uptake (VO_2) peak oxygen uptake (VO_2max) Respiratory exchange ratio (RER) Ventilatory anaerobic threshold (VT2) Carbon dioxide output (VCO_2) Heart rate (HR) Heart Rate Reserve (HRR) Breath rate at VAT Breath rate reserve (BRR) minute ventilation (VE) O_2 Pulse Heart rate variability (HRV) Exercise capacity (Borg Scale) Capillary blood gases and lactate Myocardial function At time 0 and after 6 months
Blood sample	Blood count*, Enterocytes*, Liver enzymes*, Retentionparamters*
Pulmonary tests	Lung function (VC%, FEV1%)
Clinical parameters	Age* Gender* Weight* Ethnicity* Time from therapy initiation/Interval until LF-MRI Current medication* Secondary diagnoses* Clinical examination*

*Standard procedures/parameters routinely available in follow-up care

8. Study design

Monocentric / multicentric

This is a monocentric study

Study arms: intervention/control

Patients (early and late effects) fulfilling the inclusion criteria will receive an MRI of the lungs and lung function testing

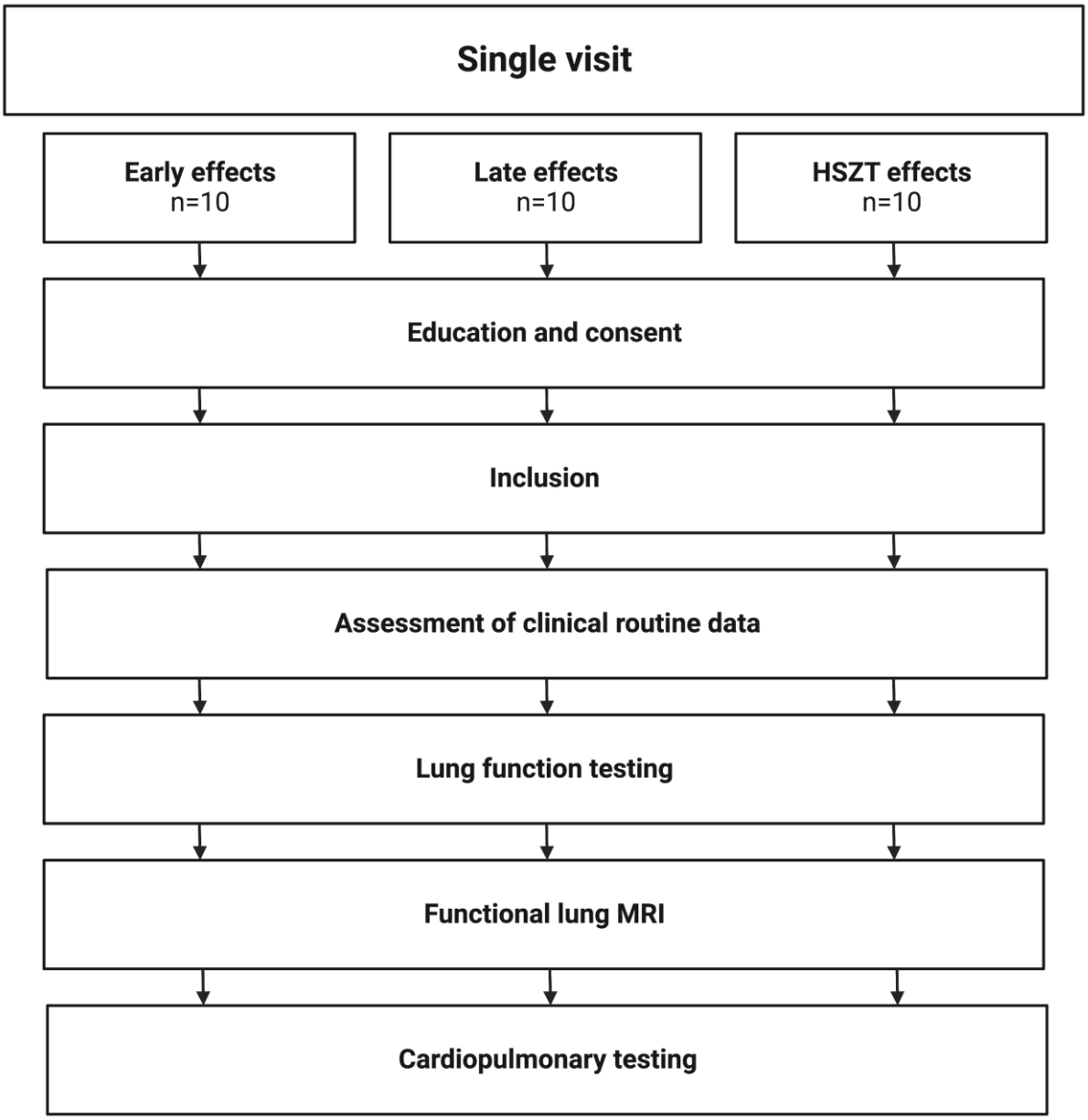
Randomization

Randomization is not planned

Blinding

Blinding to the study is not possible. Blinding of patients/subjects is not necessary

Graphical design of study flow (Patient numbers for early and late therapeutic effects are referring to each of the two patient groups with ALL and HD.)



9. Study population

In- and exclusion criteria

Early therapeutic effects	Late therapeutic effects	Effects of hematopoietic stem cell transplantation
Planned number of patients		
N=10 ALL N=10 HD	N=10 ALL N=10 HD	N=10
Inclusion criteria		
- Diagnosed acute lymphatic leukemia or Hodgkin`s disease (HD) - Completed induction therapy or radiotherapy - From 5 years to <18 years	- Diagnosed acute lymphatic leukemia or Hodgkin`s disease (HD) - Completed intensive therapy or radiotherapy - From 5 years to <18 years	- Diagnosed acute lymphatic leukemia - Completed hematopoietic ste cell transplantation - From 5 years to <18 years
Exclusion criteria		
- Pregnancy, Lactation - Known pleural or pericardial effusion - Critical condition (requiring respiratory support, ventilation, oxygen, shock, symptomatic heart failure) - Marked thoracic deformities/malformations - Previous lung surgery - Injuries that do not allow physical stress diagnostics	- Pregnancy, Lactation - Known pleural or pericardial effusion - Critical condition (requiring respiratory support, ventilation, oxygen, shock, symptomatic heart failure) - Marked thoracic deformities/malformations - Previous lung surgery - Injuries that do not allow physical stress diagnostics	- Pregnancy, Lactation - Known pleural or pericardial effusion - Critical condition (requiring respiratory support, ventilation, oxygen, shock, symptomatic heart failure) - Marked thoracic deformities/malformations - Previous lung surgery - Injuries that do not allow physical stress diagnostics

- Rejection of MRI imaging - General contraindications for MRI examinations (e.g. electrical implants such as cardiac pacemakers or perfusion pumps, etc.)	- Rejection of MRI imaging - General contraindications for MRI examinations (e.g. electrical implants such as cardiac pacemakers or perfusion pumps, etc.)	- Rejection of MRI imaging - General contraindications for MRI examinations (e.g. electrical implants such as cardiac pacemakers or perfusion pumps, etc.)

Recruitment channels and measures

Patients (and parents) will be informed about the possibility to participate in the study in public notices and announcements on the homepage of the hospital as well as when visiting the pediatric clinic for hematology and oncology (including its outpatient clinics). If patients and their parents are interested to participate, they will be fully informed about the aims and methods (especially about the scientific/explorative nature of the study), the benefits and risks, and the revocability of participation in the study before giving their consent prior to study initiation. Patients in childhood and adolescence are additionally informed and educated about the study and its procedure in an age-appropriate manner.

10. Study procedures

Procedures for informing and obtaining Consent

Patients or subjects can only be enrolled in the study after written informed consent has been obtained. The written informed consent requires an oral and written explanation to the patients/subjects, as well as their parents or legal guardians, about the aims and methods (incl. scientific-explorative character of the study), benefits and risks as well as the revocability of the study participation. Children and adolescents are informed by means of age-appropriate, comprehensible patient information sheets. By giving written informed consent, the patients/participants as well as their parents/guardians declare that they agree with the collection and storage of study-relevant data and their review by monitoring or authorities. It must be clearly conveyed to the study participant that withdrawal of consent is possible at any time and without any disadvantage. Furthermore, all study participants/subjects and parents/guardians are informed that this study is a purely scientific study without any current diagnostic or therapeutic benefit. In case of incidental findings, the study participants/test persons and parents/guardians will be informed and further clarification will be initiated if indicated.

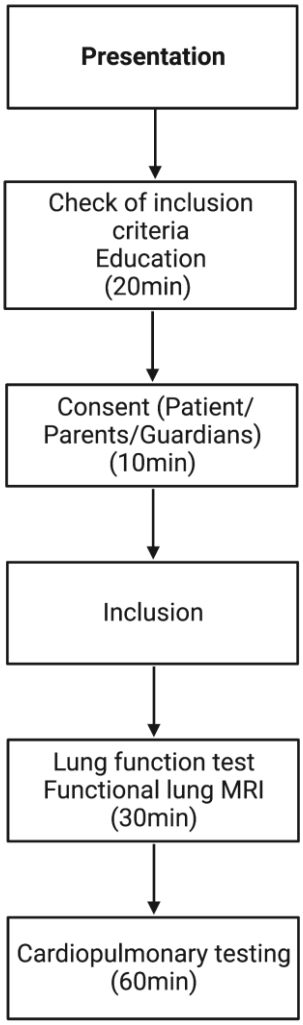
The original consent form will be kept in the study folder at the study site. The patient/proband and parent/guardian will be given a copy of the patient information and consent form. The patient information and informed consent form can be found in the appendix of this study protocol.

Study procedures

After informing the patient/proband and parents/guardians, clinical data are collected. This includes the latest laboratory analyses, which are routinely performed in these patients.

After appropriate education of parents/guardians/patient, the patients will be included. First, they undergo lung function testing (Duration approx. 10 minutes). Next, a native MRI examination (MRI examination without contrast medium administration) is performed. The duration is about 20 minutes. This is performed exclusively without sedation. Patients can remain in a lying position during the examination. During the examination, patients are protected by hearing protection from the noise generated. To enable the patient to make himself/herself heard, he/she is given a bell button shortly before the examination begins;

during the examination planning, communication is possible by means of an intercom system. In addition, the presence of a parent in the scanner room is possible during the entire examination time. The examination in the new 0.55 T MRI system does not differ in procedure and especially with regard to contraindications for an MRI examination from an examination in routinely used 1.5 or 3T devices. There is no intravenous administration of contrast medium and the images produced are not evaluated diagnostically.



During spiroergometry, the participants are subjected to a step test using treadmill spiroergometry. Spiroergometry is a non-invasive test method. However, for a better assessment of the pulmonary capacity, a blood gas analysis at rest, at the anaerobic threshold (VAT) and during exertion is a useful additional parameter, so that we are planning a capillary blood sample at these three points in time. A lancet prick in the fingertip is necessary for this. The subject then has to put on a mask during the examination, has ECG electrodes attached to the thorax and has to run for a period of around 10 minutes at increasing speed up to the limit. Time schedule and study duration for the individual subjects: approx. 60 minutes per spiroergometry.

Cardiopulmonary testing will also include echocardiographic strain and strain-rate imaging. This is a non-invasive method for the assessment of myocardial function defined as shortening or lengthening of the myocardium. This examination will take around 15 minutes. The patients lie quietly on an examination table without further measures being carried out or required.

Acquisition of target variables

- MRI imaging
- Determination of demographic data

Time schedule and duration of the study for the individual subjects/patients

For the individual patient, the duration of study participation is 120 minutes. This includes approximately 30 minutes for education and consent of study participants/parents/guardians, 30 minutes for lung function test and MRI, and 30 minutes for cardiopulmonary testing.

Total duration of the study

According to the number, the expected total duration of the study until inclusion of the last patient is approximately 18 months.

11. Benefit-risk assessment

All study-related risks

Magnetic resonance imaging

Unlike computed tomography, MRI does not use ionizing radiation, so no permanent side effects are expected. More than 1 million MRI examinations at higher field strengths (1.5/3T) are performed annually in Germany. Provided that the general contraindications for MRI examinations are observed, no serious side effects occur. MRI is therefore one of the safest examination procedures.

The risks associated with an MRI examination emanate from the three main components of the MRI system.

Static magnetic field

The static magnetic field exerts forces and torques on ferromagnetic objects that can be so strong that the (mostly ferromagnetic) objects fly uncontrollably toward the magnet and can hit patients and staff (missile effect). The magnetic forces are proportional to the field strength B and the field change with location (dB/dz). These risks are lower with the low-field MRI system. Risks are further minimized by providing safety training to operators and excluding patients with ferromagnetic implants from the study.

The gradient system

Gradient switching can cause the appearance of magnetic phosphenes and nerve and muscle cell stimulation. Fast switched gradients produce high magnetic field changes per time (dB/dt), which induce voltages in the body. If a current flows through the tissue via nerve endings, for example, this can result in so-called peripheral nerve stimulation. However, the manufacturer of the gradient system guarantees compliance with the limits for gradient switching times and amplitudes recommended in the IEC 60601-2-33 guidelines. Thus, nerve stimulation effects need not be considered further in the risk assessment of this study.

Another safety-relevant effect of gradient fields is noise caused by gradient circuits due to current- and field-strength-dependent Lorentz forces in the gradient tube. These often unpleasant loud knocking noises occur especially during fast imaging processes where high currents flow through the gradients. Noise levels can rise up to 115dB for 1.5T tomographs (background noise: approx. 78dB). Due to the lower magnetic forces at 0.5T, we expect lower

noise levels. In addition, patients always wear hearing protection during the examination, so that the noise exposure remains well below the legal limit of 99 dB.

The high-frequency system

During the MR measurement, radiofrequency (RF) fields are sent into the human body, which are partially absorbed by the tissue and can lead to an increase in body temperature. The thermoregulatory response of human tissue to RF pulses has now been studied for 50 years. For example, using conservation of energy, it has been calculated that the body temperature of lightly clothed patients with undisturbed thermoregulation at room temperature increases by up to 0.6 °C when exposed to RF at 4 W/kg (63 MHz, 1.5 Tesla). The assumed specific absorption rate (SAR) of 4 W/kg body tissue corresponds to the so-called "controlled mode first level" (IEC safety guideline), which is also used as an upper limit in routine clinical imaging. The magnitude of the actual temperature rise is generally smaller because skin cooling was not considered in the calculations (worst case scenario).

The body's energy production at rest is about 1.2 W/kg - equivalent to the energy conserved when wearing a thin sweater. Most healthy people are capable of compensating for 15 times this resting energy, and only a minimal increase in core body temperature occurs. Studies at 1.5 T have shown that RF absorption in humans leads only to the expected cardiac adaptation and does not cause adverse health effects. Theoretically, a 63 kg person is even capable of emitting 1296 W to the environment through the skin by cardiac adaptation (i.e., maximum increase in blood flow) - this would correspond to a SAR of 20.6 W/kg.

The same limits are observed with the 0.55 Tesla MRI system. At 0.55 Tesla, the wavelength of the radio waves used is significantly longer, so that the spatial distribution of the energy emission is more homogeneous and thus the risks tend to be lower.

The spiroergometry

If the infection is unknown, cardiopulmonary exertion can lead to inflammation of the heart muscles. A precise anamnesis regarding the constellation of infection as well as a clear explanation of the risks is therefore essential before exposure. A doctor is present at every examination. In addition, a risk of falling during treadmill ergometry cannot be ruled out with absolute certainty. To safely avoid injuries, the participants are secured with a safety rope.

Capillary blood sampling

The procedure of capillary blood sampling may cause additional discomfort or minor pain. Very rarely, problems with bleeding and infection can occur.

Echocardiographic strain and strain-rate imaging

This ultrasound-based non-invasive measurement will take about 15 additional minutes, during which the patient lies on an examination table. Further procedures are not required through this method. There is no additional risk is associated with this method.

Benefits associated with the study

The data obtained in the studies may provide essential insights into the long-term effects chemotherapeutics in children. Therefore, the study may influence future clinical management and therapeutic regimes.

Discontinuation Criteria

Discontinuation criteria for the individual participant:

Particularly in light of the inclusion of pediatric and adolescent participants, study participation will be discontinued if MRI cannot be performed without sedation.

Study discontinuation for the individual participant will occur if:

- an event occurs that may lead to endangerment of the patient or the staff,
- the patient withdraws consent to participate in the study, or withdraws,
- the patient does not comply with the instructions of the investigators and the operating personnel,

The patient can stop the examination at any time without giving any reason. For this purpose, a so-called bell button is available to the patient during the MRI examination, the activation of which gives a signal with which the patient can draw the attention of the physician/examiner to him/herself, even while the measurement is in progress. Furthermore, the patient is in contact with the examiner via microphone and headphones between the individual measurements and can thus also verbally request the termination of an examination. In addition, the presence of a parent in the scanner room is possible during the entire examination time. Study participants may also discontinue the study at any time before, during, and after all other study-related examinations without providing a reason.

Dropout criteria for the entire study:

There is no provision for discontinuation of the entire study.

Termination criteria for spiroergometry:

Here we follow the termination criteria of the German Spiroergometric Society or DGSP (German Society for Sports Medicine and Prevention):

• Reaching the maximum heart rate (200/min)

• No reserve of breathing available
• RER > 1.15
• Breath Equivalent > 35
• VO2 plateau despite increasing exertion (O2 rise < 150 ml/min. over 30 sec.)
• After exertion, idling for 2 minutes.
• Abnormalities in blood pressure (> 2.5 hrs above 50th percentile, sudden drop or rise)
• In treadmill ergometry with ECG: ST depression, ventricular extrasystoles

Statement on medical justifiability

The examinations will be performed exclusively on an approved MRI device using approved techniques. As the only significant difference to routinely applied MRI diagnostics, part of the data analysis will be performed with a novel software which is not yet applied in clinical practice and has not yet received the Conformité Européenne (CE) marking. The field strength used is significantly lower than the 1.5T and 3T scanners routinely used to date. The risks are low as described above, especially since no measures such as contrast agent application are foreseen. Spiroergometry is an accepted and recognized method for examining the cardiopulmonary capacity of athletes and patients. It is also used extensively in patients with severe heart and lung disease. It is now an integral part of preoperative diagnostics to assess the surgical capability of older patients. It represents a harmless and non-invasive method for estimating the cardiopulmonary capacity of patients and is therefore also easy to carry out for children.
The overall findings may help to estimate and minimalize the therapeutic risks for these patients.

The study aims at age- and disease-specific findings that cannot be derived from data from adults. The personal benefit of the study for each participant is to receive information about their individual physical (cardiopulmonary) resilience and potential secondary harm to chemotherapeutic treatments. There is no need to recruit a completely healthy comparison group.

12. Biometry

Explorative, hypothesis-generating study

Power calculation

No power calculation was performed as part of a pilot study. So far, there are no reliable preliminary data/measurements or similar to have conclusions about the frequency of possible changes. Therefore, in the context of this pilot study, a N=10 per group (patients with ALL, patients with HD, and patients after allogeneic hematopoietic stem cell transplantation) is considered reasonable.

Statistical Methodology

Continuous variables will be reported as mean with standard deviation, categorical variables as numbers with percentages if necessary. The occurrence of MRI changes is reported as a percentage of the population. All analyses are performed using GraphPad Prism (version 7.00 or later, GraphPad Software, La Jolla, CA, USA), RStudio (version 1.1.456 or later, RStudio Inc., Boston, MA, USA), or IBM SPSS Statistics (version 24 or later, IBM Corp., Armonk, NY, USA).

13. Data management and data protection

Data acquisition, storage

All raw data, such as patient records, represent source documents. Their availability is ensured for routine monitoring. Participation of individual patients or subjects in the study is documented, and the study director maintains an independent list to identify participating patients. This list included name and date of birth as well as study date and pseudonymization abbreviation of the patients and subjects. The study director is responsible for the quality of data collection and storage. Data storage (total data) is performed on computers or specially designated network drives at Erlangen University Hospital. Comparable to routine, imaging data are transferred to the protected PACS (Picture Archiving and Communication System).

Pseudonymization

Prior to any scientific analysis of the materials and data of this study, all information will be pseudonymized according to the guidelines of the German Data Protection Act.

Data transfer

The data will not be passed on to third parties.

The study results may be published anonymously, and it will not be possible to infer the identity of the participating individuals. The data will be kept for 10 years and then destroyed.

Revocation, data deletion

In case of revocation of the declaration of consent, data collected up to this point can be taken into account. The patient has the right to demand their destruction, provided that legal regulations do not prevent the destruction.

14. Handling of biomaterial

Capillary blood samples will be used for measurement of blood count, liver enzymes, and retentionparamters as standard values routinely determined supplementary to pulmonary tests available in follow-up care. These samples will not be used in a different context nor will they be stored. No additional biomaterials are obtained.

15. Insurance for partcipants

No insurance is taken out due to the low study risk.

16. Signature

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